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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/987,456	11/14/2001	Maurice Zauderer	1821.0070004/EKS/EJH/TAC	6770

26111 7590 04/21/2006

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/987,456	ZAUDERER ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *84-122 and 127-131* is/are pending in the application.

4a) Of the above claim(s) *85-87,98,100-102 and 104-106* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84,88-97,99,103,107-122 and 127-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/2/06; 10/13/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/2/06 has been entered. Claims 84-122 and 127-131 were pending (claims 1-83 and 123-126 were previously canceled). Claims 84, 86, 87, 89, 90, 91, 93-97, 107, 110, 113-120, 128, 129 and 131 were amended. No claims were added or canceled. Therefore, Claims 84-122 and 127-131 are currently pending. Claims 85-87, 98, 100-102 and 104-106 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim. Therefore, claims 84, 88-97, 99, 103, 107-122 and 127-131 are examined on the merits in this action.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. All rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 103

3. Claims 84, 88-97, 99, 103, 107-122 and 127-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) and Zauderer et al. (WO 00/28016) (Date of Patent is **May 18, 2000**) and Waterhouse et al. (Waterhouse, P.; Griffiths, A.D.; Johnson, K.S.; Winger, G. "Combinatorial infection and in vivo recombination: a strategy for making large phage antibody repertoires" *Nucleic Acids Research*, **1993**, 21, 9, 2265-2266).

For ***claims 84, 88, 96-97, 113, 117***, Rowlands et al. (see entire document) teach a method for producing antibodies in vaccinia infected cells that reads on the presently claimed invention (e.g., see Rowlands et al., abstract). For example, Rowlands et al. teach **[a-c]** the use of a population of mammalian host cells (e.g., see page 4, paragraph 2; see also paragraph bridging pages 7-8) for introducing and expressing a first/second polynucleotide encoding, through operable association with a transcriptional control region a first/second immunoglobulin polypeptide comprising both heavy/light chain constant/variable regions and a signal peptide for secretion using a vaccinia virus vector (e.g., see claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant

domain at the other end"; see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"; see also page 6, paragraphs 1 and 2). Rowlands et al. do not explicitly state that a "signal" peptide is being used, but the Examiner contends that this feature is inherent in the method disclosed by Rowlands et al. because the fully functional recombinant antibody would not be "secreted" unless it has such a sequence. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

In addition, Rowlands et al. disclose **[d]** contacting said immunoglobulin molecules with an antigen and detecting specific antigen-antibody complexes (e.g., see pages 18-19 and Table I wherein the Campath 1H antigen was "contacted" with said immunoglobulin molecules and "detection" was carried out using both T-cell and antigen binding assays). Finally, Rowlands et al. disclose **[e]** recovering the vaccinia virus vectors containing polynucleotides of said first library which encode immunoglobulin subunits polypeptides which, as part of an immunoglobulin molecule are specific for said

antigen (e.g., see page 5, paragraph 1, step 4, wherein the virus is "harvested" several times [i.e., recovered and/or isolated]).

For ***claim 103***, Rowlands et al. disclose a T7 phage promoter active in cells in which T7 RNA polymerase is expressed (e.g., see page 8, paragraph 2, "Expression levels of the two chains of the antibody can be enhanced by use of T7 polymerase to amplify the gene under the control of the T7 promoter").

For ***claims 121-122***, Rowlands et al. disclose ELISA (e.g., see page 18, line 7).

The prior art teachings of Rowlands et al. differ from the claimed invention as follows:

For ***claim 84***, Rowlands et al. are deficient in that they do not specifically teach the use of a "library" of first/second polynucleotides.

For ***claims 89-91***, Rowlands et al. do not disclose repetitive steps for "biopanning" a library.

For ***claims 92-95***, Rowlands et al. do not provide "isolating" steps.

For ***claim 99***, Rowlands et al. do not disclose an MOI of 1.

For ***claim 107, 110, 127-131***, Rowlands et al. do not disclose method steps for "tri-molecular" recombination.

For ***claims 108-109, 111-112***, Rowlands et al. do not disclose v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction sites.

For ***claims 114-116, 118-120***, Rowlands et al. do not disclose the use of virus "pools."

However, Zauderer et al. and Waterhouse et al. teach the following limitations that are deficient in Rowlands et al.:

For ***claim 84***, Zauderer et al. (see entire documents) teach the use of a "library" of polynucleotides in a vaccinia virus vector using the "tri-molecular recombination" approach for screening purposes (e.g., see Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52). In addition, Waterhouse et al. teach that a "library" can be usefully employed to screen for antibodies with high affinity to various antigens including the use of heavy/light chains that are "packaged together" i.e., two libraries (see Waterhouse et al., page 2265, column 1; see also paragraph bridging pages 2265-2266, "... creation of extremely large combinatorial repertoires [is possible]... for example by providing a light chain repertoire in A [i.e., library number 1] and a heavy chain repertoire in B [i.e., library number 2]"). The Examiner further notes that Applicants' elected mammalian "HeLa" cells are disclosed also by Zauderer et al. (e.g., see Zauderer et al., page 32, line 2).

For ***claims 89-91***, Zauderer et al. disclose the use of vaccinia virus library vectors that require the use of a helper virus (i.e., are "incapable of producing infectious vaccinia virus") to infect host cells (e.g., see Zauderer et al., paragraph bridging pages 97-98, "Vaccinia virus DNA is not infectious as the virus cannot utilize cellular transcriptional machinery ... Previously ... non-homologous poxvirus fowlpox ... have been utilized as

helper virus for packaging"). Zauderer et al. also indicate that the steps for introducing said vectors into host cells, permitting the expression of said vectors, contacting said expressed antibodies with an antigen and recovering said vectors can be repeated as needed to increase the specificity and/or binding affinity (e.g., see page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure").

For ***claims 92-95***, Zauderer et al. disclose "isolating" the polynucleotides contained in the vaccinia virus vectors (e.g., see Zauderer et al., page 52, lines 20-23; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

For ***claim 99***, Zauderer et al. disclose, for example an MOI = 1 (e.g., see page 86, line 2).

For ***claims 107, 110, 127-131***, Zauderer et al. disclose "tri-molecular" recombination, which includes, for example, cleavage of v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction enzymes and "one" transfer plasmid containing TKL/TKR and a library of human immunoglobulin genes containing both heavy and light genes to form vaccinia virus vectors via homologous recombination and method steps for screening and purifying said vectors repeated as many times as are needed to produce the desired products (e.g., see pages 48-52, sections 5.2-5.3; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e.,

involves combining isolated fractions]"; see also claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter").

For ***claims 108, 111***, Zauderer et al. disclose both v7.5/tk and vEL/tk (e.g., see figure 1).

For ***claims 109, 112***, Zauderer et al. disclose both NotI and ApaI (e.g., see figure 10).

For ***claims 114-116, 118-120***, Zauderer et al. disclose the use of "virus pools" (e.g., see page 51, last paragraph, especially line 27; see also page 58, Table V wherein multiple cycles are disclosed; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

It would have been obvious to one skilled in the art at the time the invention was made to make a library of vaccinia virus vectors as taught by Zauderer et al. to express fully functional antibodies as taught by Rowlands et al. for the purpose of screening and/or affinity maturation as taught by Waterhouse et al. because Zauderer et al. explicitly state that their libraries can be efficiently produced using the tri-molecular recombination approach with the vaccinia virus vectors (like the vaccinia virus vectors disclosed by Rowlands et al.) and Waterhouse et al. teach that such a library would be useful in screening and affinity maturation. Thus, one of ordinary skill in the art would

have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"; see also Rowlands et al., page 4, paragraph 2, "One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian origin"). In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" (e.g., see Waterhouse et al., page 2265, paragraph 2; see also page 2265, column 1; see also paragraph bridging pages 2265-2266 wherein the usefulness of combinatorial antibody libraries is disclosed), which would encompass the "associated" heavy/light chains described by Rowlands et al. In addition, Waterhouse et al. also teach that larger "primary" repertoires of antibodies "should allow higher affinity fragments to be isolated" (e.g., see Waterhouse et al., page 2265, column 1, paragraph 1; see also page 2266, column 1, paragraph 1), which can be easily produced by varying providing "a light chain repertoire in A and a heavy chain repertoire in B" (i.e., producing two libraries simultaneously). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Zauderer et al. teach several

successful examples of library formation using the same vaccinia virus vectors that are disclosed by Rowlands et al. and Waterhouse et al. teach several successful examples of associated light/heavy chains that can be used for screening and/or antibody maturation, which would encompass the heavy/light chain antibodies disclosed by Rowlands et al. In addition, Rowlands et al. state that the use of vaccinia virus as vectors is well known and has wide applications and explicitly state that it can be used for antibody production (e.g., see Rowland et al., page 4, first full paragraph, "The use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a decade ..."; see also paragraph bridging pages 9 and 10, "the versatility of the method to the present invention means that it will usually be possible to select a type of cell that carries out the processing necessary to produce a fully functional antibody").

Response

4. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered including all exhibits and/or declarations (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "... the Examiner has essentially repeated the same arguments as set forth in the previous Office Action, dated April 21, 2005. In response, Applicants reiterate and maintain their arguments as set forth in Reply field on July 21, 2005" (e.g., see 2/2/06 Response, page 19, last paragraph).

[2] Applicants argue that the Examiner has mischaracterized their statements in the previous office action and assert that the combined references do not teach the introduction of two expression libraries into eukaryotic host cells. According to Applicants, "Waterhouse (not the combined references) discloses the introduction of bacteriophage vectors encoding immunoglobulin heavy and light chain variable region fragments ... into bacterial, i.e., prokaryotic, host cells, and suggests that this prokaryotic system can be used to generate large combinatorial libraries by providing repertoires of heavy and light chain fragments ... [However] Applicants respectfully maintain and emphasize that the cited references do not teach or suggest the introduction of two expression libraries into eukaryotic host cells for selecting antigen-specific human immunoglobulin molecules" (e.g., see 2/2/06 Response, page 20, especially last paragraph).

[3] Applicants argue, "there is no motivation or suggestion for one of ordinary skill in the art to combine these reference to introduce two expression libraries encoding immunoglobulin subunit polypeptides into eukaryotic cells for selecting polynucleotides which encode an antigen-specific human immunoglobulin molecule because Rowlands disclose the expression of a previously selected antibody (i.e., not separate, randomly introduced libraries of immunoglobulin light and heavy chains), and Zauderer discloses the introduction of a single expression library into eukaryotic host cells (i.e., not two separate expression libraries of immunoglobulin light and heavy chains)" (e.g., see 2/2/06 Response, page 21, especially last paragraph).

[4] Applicants argue, "... the 'associated heavy and light chains' in Rowlands are not the same as the 'associated heavy and light chains' that can be 'simultaneously co-selected' in Waterhouse ... [and] are different from the present invention ... Rowlands demonstrated the

expression of a single antibody that had already been selected for heavy and light chains that paired correctly and efficiently ... Waterhouse, on the other hand, describes simultaneous co-selection of antibody heavy and light chain fragments from prokaryotic host cells ... this type of co-selection of heavy and light chain fragments expressed from a common vector does not teach or suggest that heavy and light chains would associate to form an antigen-specific immunoglobulin as in the present invention ... wherein separate, random heavy and light chain libraries in separate vectors are introduced into eukaryotic cells ... (e.g., see 2/2/06 Response, pages 22 and 23, especially page 23, paragraph 1).

[5] Applicants argue, "[According to the Storkus Declaration] random pairs of immunoglobulin heavy and light chains derived from separate eukaryotic expression libraries would be expected to be poorly matched" and thus one would not expect "that antigen-specific antibodies could be efficiently selected from random libraries of immunoglobulin heavy and light chains expressed in eukaryotic cells in vitro" (e.g., see 2/2/06 Response, pages 23, paragraph 1, see also Storkus Declaration, especially pages 3 and 4).

[6] Applicants argue that the Examiner is using Applicants' specification as a "blueprint" to select only those features that will support the obviousness rejection and thus impermissible "hindsight reconstruction" has been used (e.g., see 2/2/06 Response, pages 23 and 24).

[7] Applicants argue, "As with respect to the Warnick reference in *Fine*, the present invention diverges from Waterhouse and teaches advantages not appreciated or contemplated by it. Namely, the methods of the present invention are performed using eukaryotic cells and allow selection of an immunoglobulin of interest by introducing two separate, expression libraries of heavy and light chains in eukaryotic host cells. The advantages of performing immunoglobulin

screening and selection in eukaryotic cells are discussed in detail in the Declaration of Dr. Maurice Zauderer" (e.g., see 2/2/06 response, pages 24 and 25).

[8] Applicants argue that relying on Waterhouse for the proposition that co-selection will lead to more favorable antibodies "regardless" of the how the antibodies are produced is improper because it fails to consider the reference as a whole. In particular, it "ignores the fact that the methods disclosed in Waterhouse are performed in prokaryotic system[s]" (e.g., see 2/2/06 Response, page 26, last paragraph).

[9] Applicants argue, "Dr. Storkus stated in his Declaration that methods using prokaryotic expression systems could not be extrapolated to eukaryotic cells because the conditions for assembly of immunoglobulins from light and heavy chains are different in the eukaryotic cytoplasm than in the periplasmic space of a bacterial host, and that it could not be known what effect this would have on antibody assembly." (e.g., see 2/2/06 Response, page 27, paragraph 2, internal quotations omitted; see also Storkus declaration, especially page 4).

[10] Applicants contend that they are not arguing the references individually and maintain that the combined references do not teach all the claimed limitations (e.g., see 2/2/06 Response, pages 27 and 28).

[11] Applicants argue, "[t]he present case is analogous to Hybritech in that, here, the Examiner is focusing on the notion that a prokaryotic expression library system for selecting antibody fragments with heavy and light chain components as disclosed in Waterhouse can simply be substituted by a eukaryotic system for selecting polynucleotides encoding antigen specific immunoglobulins or fragments as in the present invention. As established in *Hybritech*,

this is an improper analysis for establishing a prima facie case of obviousness." (e.g., see 2/2/06 Response, pages 28-30, especially page 29, second paragraph).

[12] Applicants argue, "the opposing evidence for supporting an obviousness rejection is not strong" and refer to Items [1] to [3] and [5] to [7] in support of this argument.

[13] Applicants argue, " Dr. Zauderer states that one of ordinary skill in this art would not have been motivated to combine Waterhouse with Rowlands and Zauderer because Waterhouse discloses a method for providing repertoires of antibody light and heavy chain fragments in the context of phage display ... According to the Zauderer Declaration, one of ordinary skill in the art would not have considered the features disclosed in Waterhouse as something that could be expanded for use in eukaryotic systems" (e.g., see 2/2/06 Response, page 31, paragraph 1).

[14] Applicants argue that the long felt need should be analyzed from the date the problem is identified and articulated, not as of the date of the most pertinent prior art and, as a result, the Zauderer reference is not the proper date for measuring the long-felt need (e.g., see 2/2/06 Response, pages 32 and 33). See also MPEP § 716.04.

[15] Applicants argue, "The need in the art for a method of selecting polynucleotides ... was well known. Paragraphs [0003] to [0010] of the present specification and paragraphs 8, 9, 16, and 17 of the Zauderer Declaration summarize the nature of the problem in the art in isolating antigen-specific human antibodies using the alternative technologies ... Evidence of the problems in the art and the long-felt need for the solution provided by the claimed invention is also found in the excerpt of the document entitled 'Monoclonal Antibody Partnerships in the biopharmaceutical Industry,' which was referenced in the Storkus Declaration as exhibit A2. Applicants further point to page 29 of A2, which states "... We have been evaluating MAb

companies for research and therapeutic uses for awhile now and we have yet to make a decision. None of the companies are a clear winner ... ." Applicants also reference exhibits B2 to B4 and talk about the press releases that announced collaborations between Vaccinex, Inc. and various other companies that are interested in producing antigen-specific human monoclonal antibodies for therapeutic and diagnostic purposes (e.g., see 2/2/06 Response, pages 33 and 34).\

[16] Applicants argue, "[c]ontrary to the Examiner's assertions, Applicants arguments that there was a long-felt need for the present invention are not obviated by the fact that the previously available technologies sometimes worked and sometimes did not, with unpredictable reliability" and, presumably as a result, Applicants arguments don't have to be commensurate in scope with the claims (e.g., see 2/2/06 Response, page 34).

[17] Applicants argue, "[a]s explained in detail in Items [2] and [3], supra, this analysis fails to consider the invention as a whole" (e.g., see 2/2/06 Response, page 35, paragraph 1 to page 36, paragraph 1").

[18] Applicants argue that there is no expectation of success and cite *In re Vaeck* in support of this conclusion stating, "[u]nlike in *Vaeck*, the eukaryotic host cells in the method of the present invention and the prokaryotic host cells used in the phage display methods in Waterhouse are not even in the same taxonomic kingdom. Hence, the differences between the cited reference and the claimed invention in the present case are even greater than those in Vaeck" (e.g., see 2/2/06 Response, pages 36 and 37, especially page 37, paragraph 2).

[19] Applicants argue that the Examiner has only established that it might be "obvious to try" the claimed invention (e.g., see 2/2/06 Response, page 37, paragraph 3).

[20] Applicants argue, "these excerpts from the Applicants' Reply were made with respect to the efficiency of insertion of heterologous nucleic acid sequences into vectors in methods by which expression libraries, not antibodies, are generate" and, presumably as a result, the "commensurate in scope" argument has been refuted (e.g., see 2/2/06 Response, especially, page 38, middle paragraph).

[21] Applicants argue, "If the immunoglobulin chains do not pair in such a way that they do not produce molecules that specifically bind an antigen, and therefore cannot be selected then they would not be antigen-specific. Thus, Applicants respectfully submit that the Storkus Declaration provide evidence that is commensurate with the scope of the claims (e.g., see 2/2/06, Response, pages 38 and 39; see also Storkus Declaration, especially page 3).

[22] Applicants respectfully direct the Examiner's attention to sections [1] to [5] to refute the prima facie case (e.g., see 2/2/06 Response, page 39, paragraph 2).

[23] Applicants argue, "As set forth in Item [6], supra, the excerpts from Applicants' Reply are inapposite to the Examiner's argument because they do not address antibody quality ... Furthermore ... as set forth in Items [4] and [6] ..." (e.g., see 2/2/06 Response, pages 39 and 40).

[24] Applicants argue, "... it is not necessary that the claimed invention recite limitations that reflect, for example, all of the specific antigenic targets in which anyone who licenses the claimed invention may be interested in order for the Exhibits to have probative value as objective evidence of nonobviousness. Rather, it is sufficient that numerous business organizations are interests in using the claimed technology to fill a need that was not met by the prior art methods." (e.g., see 2/2/06 Response, page 40, last paragraph).

[25] Applicants argue, "the Examiner seems to be conflating the idea of showing the existence of licenses by competitors in a market to establish commercial acquiescence, as a secondary indicator of non-obviousness ... with the use for which Applicants submitted Exhibits B2 to B4, which is to show that various business organizations are interested in entering strategic alliances to use the claimed invention because the prior art technologies were unsuitable for their needs" (e.g., see 2/2/06 Response, page 41, paragraph 1).

This is not found persuasive for the following reasons:

[1, 12, 17, 22, 23] To the extent that Applicants are simply repeating their previous arguments, those arguments were adequately addressed in one of the previous office actions or one of the cited sections cited by Applicants, which are incorporated in their entirety herein by reference.

[2] "[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968) (A process for catalytically producing carbon disulfide by reacting sulfur vapor and methane in the presence of charcoal at a temperature of "about 750°-830°C" was found to be met by a reference which expressly taught the same process at 700°C because the reference recognized the possibility of using temperatures greater than 750°C. The reference disclosed that catalytic processes for converting methane with sulfur vapors into carbon disulfide at temperatures greater than 750°C (albeit without charcoal) was known, and that 700°C was "much lower than had previously proved feasible."); *In re Lamberti*, 545 F.2d 747, 750, 192 USPQ 278, 280 (CCPA 1976) (Reference disclosure of a compound where the R-S-R'; portion

has "at least one methylene group attached to the sulfur atom" implies that the other R group attached to the sulfur atom can be other than methylene and therefore suggests asymmetric dialkyl moieties."). Here, it can be inferred from Waterhouse that in order to receive the benefit of simultaneous co-selection two libraries are going to have to be introduced (i.e., heavy and light chain) into an expression system because co-selection would not occur without diversity in both the heavy (i.e., library 1) and light (i.e., library 2) chains. Thus, the Waterhouse teachings of "two" antibody libraries (i.e., heavy and light chains) would extend to both prokaryotic and eukaryotic systems because "antibody" libraries (with heavy and light chains) are being produced in both cases. Furthermore, the combined teachings of Rowlands et al. and Zauderer et al. teach a facile method for producing expressing such combinatorial libraries in a eukaryotic system.

That is, a person of skill in the art (most likely a Ph.D.) working in the field of immunology and/or combinatorial chemistry (i.e., for the purpose of producing antibody and/or antibody libraries) would look to all relevant papers for guidance (e.g., papers encompassing phage display, vaccinia virus, etc.) because the problems encountered are not "unique" to any one system. The advantages obtained from producing large "primary" libraries of heavy and light chains (i.e., two libraries) and the advantages associated with being able to co-select these heavy and light chains in order to produce, for example, antibodies with high affinity are just as applicable to mammalian expression systems as they are to phage display. The products in each case (i.e., the antibodies or antibody libraries) would be the same. Furthermore, Applicants' own specification makes clear that a person of skill in the art would routinely look at a wide variety of expression systems for guidance (e.g., see specification, page 2 and 3, "Previously, three general

strategies have been employed to produce immunoglobulin molecules ... In one approach, rodent antibody sequences have been converted into human antibody sequences, by grafting ... An alternative approach, which does not suffer this same limitation, is to screen recombinant human antibody fragments displayed on bacteriophage"). Thus, Applicants' arguments for a per se rule that a person of skill in the art would never combine the teachings of a "phage display" reference with a "vaccinia virus" reference even if both references teach a method for producing antibodies is not persuasive. Both papers deal with the production of antibodies and, as a result, represent analogous art (e.g., see *In re Paulsen* 31 USPQ2d 1671 (Fed. Cir. 1994) (A "clam style" fastening means is not "unique" to the computer industry and, as a result, a person of skill would consult other "mechanical" literature for a solution to this fastening problem). Furthermore, in response to applicant's arguments against the Waterhouse et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[3] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by

Rowlands et al. because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"). In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" (e.g., see Waterhouse et al., page 2265, paragraph 2; see also page 2265, column 1; see also paragraph bridging pages 2265-2266 wherein the usefulness of combinatorial antibody libraries is disclosed), which would encompass the "associated" heavy/light chains described by Rowlands et al. In addition, Waterhouse et al. also teach that larger "primary" repertoires of antibodies "should allow higher affinity fragments to be isolated" (e.g., see Waterhouse et al., page 2265, column 1, paragraph 1; see also page 2266, column 1, paragraph 1), which can be easily produced by varying providing "a light chain repertoire in A and a heavy chain repertoire in B" (i.e., producing two libraries simultaneously).

Furthermore, in response to applicant's arguments against the Rowlands reference individually (or in combination with Zauderer), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, two separate expression libraries of both immunoglobulin light and heavy chains is clearly suggested by Waterhouse (e.g., see section [2] above).

[4] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the use of "separate vectors", the use of libraries that are not "poorly matched"; the use of libraries that have not been "already been selected for heavy and light chains that paired correctly and efficiently" are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). For example, independent claim 84 fails to disclose the use of "separate" vectors stating, "wherein said first library is constructed in a vaccinia virus vector ... and wherein said second library is constructed in a vaccinia virus vector." That is, claim 84 doesn't state, "wherein said first library is constructed in a vaccinia virus vector ... and wherein said second library is constructed in a separate vaccinia virus vector." Furthermore, the claim 84 does not even address the efficiency with which the "matching" should occur. Finally, claim 84 does not mention anything about whether or not the antibodies need to be "pre-selected" for proper pairing or not. Thus, Applicants arguments are not commensurate in scope with the claims.

In addition, the combined references of Rowlands et al., Zauderer et al. and Waterhouse et al. do teach the use of "separate" vectors (e.g., see Rowlands et al., abstract; see also page 6, paragraph 1, "Where a recombinant vaccinia virus is produced containing DNA capable of expressing only one chain (the light chain or the heavy chain) of an antibody, then it will be necessary to co-infect the host cells with another recombinant vaccinia virus containing DNA capable of expressing the other chain").

[5] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "efficient" selection, libraries that are not "poorly matched", the use of "random" pairs of immunoglobulins) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In addition, the Declarations under 37 CFR 1.132 filed 7/21/05 are insufficient to overcome the rejection of claims 84, 88-97, 99, 103, 107-122 and 127-131 based upon 35 U.S.C. 103(a) as set forth above because:

Applicants' arguments are not commensurate in scope with the claims (e.g., see *In re Grasselli*, 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir. 1983) (Claims were directed to certain catalysts containing an alkali metal. Evidence presented to rebut an obviousness rejection compared catalysts containing sodium with the prior art. The court held this evidence insufficient to rebut the prima facie case because experiments limited to sodium were not commensurate in scope with the claims); see also *In re Tiffin and Erdman*, 171 USPQ 294 (CCPA 1971) and cases cited therein; see also MPEP § 716.02(d). The claims do not require "efficient" introduction of libraries into hosts cells, "efficient" selection, libraries that are not "poorly matched", the use of "random" pairs of immunoglobulins or the production of "good" antibodies as Dr. Storkus contends. For, independent claim 84 does not set any requirements on the "efficiency" of selection or the resultant quality of the antibody libraries produced. Thus, Applicants arguments are not commensurate in scope with the claims. In addition, Applicants make clear that low efficiency methods that generate poor antibodies are also to be included within the scope of

Applicants' claims (e.g., see 12/7/04 Response, page 22, "While the specification does indicate that direct ligation results in a relatively low recombination efficiency and titer ... it does not say that methods such as direct ligation or modified homologous recombination [which are included within the scope of Applicants' invention] cannot be used to generate vaccinia virus expression libraries"; see also page 25, first full paragraph, "... direct ligation and modified homologous recombination may be less efficient than tri-molecular recombination ... [however] the specification does not say that they cannot be used").

Furthermore, there is no requirement that the antibodies "associate properly in the cytoplasm" (e.g., see claim 84 wherein the polypeptides only need be "capable of" combining together) and any underlying facts to support this contention, which have not bee set forth by Dr. Storkus, have been refuted by the combined teachings of Rowlands et al., Zauderer et al. and Waterhouse et al., which clearly sets forth successful examples of the proper association of heavy and light chains (e.g., see page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"). In fact, Applicants' go so far as to state that only "two" antibodies need be produced by the claimed method, which clearly does not constitute a useful screen (e.g., see 12/7/04 Response, page 24, "... claim 84 ... requires expression of a 'plurality' of different immunoglobulins, i.e., two or more different immunoglobulins" see also footnote 3 on page 24) (emphasis added). In addition, Applicants' claims are not even limited to antibodies. For example, claim 84 states that the polypeptides merely must be "capable" of combining.

In addition, applicant's assertion is contrary to the record where, for example, the combined references of Rowlands et al., Zauderer et al. and Waterhouse et al. explicitly state that a light and heavy chain antibody will combine to form a recombinant antibody (e.g., see Rowlands et al., page 4, middle paragraph, "It has not been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form") (emphasis added).

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

[6] In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

[7] The Examiner respectfully disagrees. Applicants have mischaracterized the holding in *Fine*. *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988), involved a system for measuring minute quantities of nitrogen presumably for the detection of drugs and explosives. The claims were rejected as being obvious over Eads in view Warnick. Eads disclosed a method for separating and identifying sulfur compounds. Warnick disclosed a process for detecting pollutants in the

atmosphere by measuring the level of nitric oxide. The PTO held that it would have been *prima facie* obvious to substitute the nitric oxide detector of Warnick for the sulfur dioxide detector of Eads. On appeal, the Federal Circuit reversed noting that Eads deliberately sought to avoid the use of nitrogen because the sulfur detector was adversely affected by substantial quantities of nitrogen. Thus, according to the CAFC, "instead of suggesting that the system be used to detect nitrogen compounds, Eads deliberately seeks to avoid them; it warns against rather than teaches Fine's invention." See *Id.* at 1599. Thus, *In re Fine* provides an example of a "teaching away" by disclosing that the presence of a claimed element, nitrogen, is undesirable. Thus, *In re Fine* is distinguishable from the present case. No such "teaching away" exists here. To the contrary, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"; see also Rowlands et al., page 4, paragraph 2, "One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian origin"). In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" (e.g., see Waterhouse et al., page 2265, paragraph 2; see also page 2265, column 1; see also paragraph bridging pages 2265-2266

wherein the usefulness of combinatorial antibody libraries is disclosed), which would encompass the "associated" heavy/light chains described by Rowlands et al. In addition, Waterhouse et al. also teach that larger "primary" repertoires of antibodies "should allow higher affinity fragments to be isolated" (e.g., see Waterhouse et al., page 2265, column 1, paragraph 1; see also page 2266, column 1, paragraph 1), which can be easily produced by varying providing "a light chain repertoire in A and a heavy chain repertoire in B."

In addition, the Examiner notes, "there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention" (see MPEP § 2144).

[8] The Examiner respectfully disagrees. A reference is good for all it teaches to one of ordinary skill in the art, *In re Fritch*, 972 F.2d 1260, 1264, 23 USPQ2d 1780, 1782 (Fed. Cir. 1992), and is not limited to the particular invention described and to be protected by the patent, *EWP Corp. v. Reliance Universal Inc.*, 755 F.2d 898, 907, 225 USPQ 20, 25, (Fed. Cir.1985), the specific examples disclosed, *In re Fracalossi*, 681 F.2d 792, 794 n.1, 215 USPQ 569, 570 n.1 (CCPA 1982); *In re Lamberti*, 545 F.2d 747, 750, 192 USPQ 278, 280 (CCPA 1976), or preferred embodiments. *In re Mills*, 470 F.2d 649, 651, 176 USPQ 196, 198 (CCPA 1972). Here, the Waterhouse reference, when taken as a whole, impliedly teaches the advantages of using co-selection to produce more favorable antibodies "regardless" of the method of production. That is, producing high affinity antibodies does not depend on the phage expression system but, rather, on the size of the library that can be created with that expression system (e.g., see Waterhouse, page 2265, column 1, paragraph 1, "However larger 'primary' repertoires of phage antibodies should allow higher affinity fragments to be isolated [i.e., the increased size of the library increases affinity]"). This is a general theme in screening because finding the right

antibody depends, in part, on producing that antibody and if that antibody is never produced (i.e., a small library) then it cannot be selected for in the screening assay. Packaging heavy and light chains together increases the size and diversity of the library and also allows for a more realistic presentation of the ligand. These benefits (i.e., the increased size of the library, the increased diversity of the library, the presentation of both VH and VL chains to the antigen) are not going to change when the expression system is altered from prokaryotic to eukaryotic because as mentioned at length these benefits are independent of the expression system.

[9] Obviousness does not require absolute predictability of success; rather, all that is required for obviousness under § 103 is a "reasonable expectation of success." *In re O'Farrell*, 853 F.2d at 903-904 [7 USPQ2d at 1681]. Here, Rowlands et al. teach a method for producing antibodies in vaccinia infected "mammalian" cells (e.g., see Rowlands et al. page 4, paragraph 2; see also paragraph bridging pages 7-8). Thus, the conclusion that a person of skill in the art would know how to express an antibody in a "mammalian" cell is reasonable. Zauderer et al. teach how to make and/or use a library of proteins using a vaccinia virus vector like the vaccinia virus vector disclosed by Rowlands (e.g., see Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52). Thus, the conclusion that a person of skill in the art would know how to make and/or use a library of proteins, including antibodies, with a vaccinia virus is reasonable. The Zauderer et al. reference never states or indicates in any way that the use of tri-molecular recombination should somehow limited to expressing only one particular class of proteins (i.e., everything but

Applicants' claimed antibodies). Furthermore, the prokaryotic/eukaryotic distinctions to which Applicants refer (e.g., see 7/21/05 Response, paragraph bridging pages 22 and 23) are not at issue in this case. The Waterhouse et al. reference is not being relied upon for the purpose to which Applicants allude. The Examiner has never contended that the eukaryotic systems should somehow employ prokaryotic reaction conditions in some sort of hybrid expression system. The Waterhouse et al. reference, when take as a whole, impliedly shows that the production of two libraries (e.g., heavy and light chain) will lead to more favorable antibodies via a co-selection process regardless of how those antibodies are produced. Thus, Applicants' arguments are moot.

Furthermore, the Storkus declaration has been afforded little if any patentable weight for the reasons set forth in [5] above, which is incorporated in its entirety herein by reference.

[10] The Examiner likewise maintains that Applicants are arguing the references individually and further maintains that all the limitations are met for the reasons of record and as expressed in the rejection above.

[11] The Examiner respectfully disagrees. Applicants have mischaracterized the holdings in *Hybritech*. In *Hybritech Incorporated v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (CAFC 1986), the claims at issue were directed to immunometric assays using monoclonal antibodies having a specified affinity. See *Id.* at 83 (wherein claim 19, the broadest claim, sets forth, "an immunometric assay to determine the presence or concentration of an antigenic substance in a sample of a fluid ... the improvement comprising employing monoclonal antibodies having an affinity for the antigenic substance of at least about 10^8 liters/mole"). The claims were upheld, in part, because four of the most important references that were used to invalidate these claims in the district court, according to the CAFC, did not constitute prior art. See *Id.* at 90-91 ("First, the

latest four of the eight articles that the court stated were of the "utmost importance" because they "predicted" that the breakthrough in production of monoclonal antibodies by Kohler and Milstein would lead to widespread use of monoclonal antibodies in immunoassays are neither 102(a)/103 nor 102(b)/103 prior art because they are dated between late 1979 and March 6, 1980, well after the date of conception and within one year of the filing date of the '110 patent."). According to Judge Rich, none of the remaining articles suggested the use of monoclonal antibodies in sandwich assays. See *Id.* at 91 ("The earliest four of the eight articles ... discuss production of monoclonal antibodies ... but none discloses sandwich assays. At most, these articles are invitations to try monoclonal antibodies in immunoassays but do not suggest how that end might be accomplished."). That is not the case here. The Waterhouse et al. reference constitutes prior art and it expressly or impliedly teaches the use of antibody co-selection.

In addition, *Hybritech* had set forth evidence of commercial success supporting a conclusion of nonobviousness. The patentee's assays had become a market leader within a few years taking approximately 25% of the market. In addition, the evidence of advertising did not show absence of a nexus between commercial success and the merits of the claimed invention because spending 25-35% of sales on marketing was not inordinate (mature companies spent 17-32% of sales in this market), and advertising served primarily to make industry aware of the product because this is not kind of merchandise that can be sold by advertising hyperbole. See MPEP § 7163.03(b). This is also not the case here. The Examiner finds Applicants' secondary evidence to be non-persuasive for the reasons of record.

Thus, the present case is distinguishable from *Hybritech* because Waterhouse expressly or impliedly teaches the benefits of using antibody libraries that would be just as applicable to

eukaryotic systems and prokaryotic systems. In *Hybritech*, the CAFC removed the references four references that provide the motivation to substitute monoclonal for polyclonal antibodies.

[13] The Declarations under 37 CFR 1.132 filed 7/21/05 are insufficient to overcome the rejection of claims 84, 88-97, 99, 103, 107-122 and 127-131 based upon 35 U.S.C. 103(a) as set forth above because:

As stated previously, "In assessing the probative value of an expert opinion, the examiner must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion." (e.g., see MPEP § 716.01(c)). Here, Applicants provide no factual evidence. The interest of the expert in the outcome is great (i.e., it's the expert's application at issue). The opposing evidence is strong for the reasons stated in the newly amended rejection above. Finally, the nature of the matter, which Applicants are trying to establish, pertain only to legal conclusions (e.g., no motivation to combine, no reasonable expectation of success, etc.) that have been set forth in an entirely conclusory manner and thus should be afforded little or no weight (e.g., see *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement"). In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Although Applicants state that Dr. Zauderer provides more than a legal conclusion they do not point to any facts or evidence other than the author's conclusory opinion. Furthermore, obviousness does not require absolute predictability of success; rather, all that is required for

obviousness under § 103 is a "reasonable expectation of success." In re O'Farrell, 853 F.2d at 903-904 [7 USPQ2d at 1681]. Here, a person would have reasonably expected to be successful because the combined teachings of Zauderer et al. and Rowlands et al. teach how to express a libraries of antibody heavy and light chains in a eukaryotic vaccinia virus host. In addition, Dr. Zauderer's argument for a per se rule that a person of skill in the art would never combine the teachings of a "phage display" reference with a "vaccinia virus" reference even if both references teach a method for producing antibodies is not persuasive. Both papers deal with the production of antibodies and, as a result, represent analogous art (e.g., see *In re Paulsen* 31 USPQ2d 1671 (Fed. Cir. 1994) (A "clam style" fastening means is not "unique" to the computer industry and, as a result, a person of skill would consult other "mechanical" literature for a solution to this fastening problem). Furthermore, Applicants' own specification classifies phage display as "related art" (e.g., see specification, page 1, "Related Art" section, see especially pages 3 and 4, paragraphs 7 and 8).

[14] Applicants have misinterpreted the Examiner's arguments. The Examiner has never asserted that the long felt need should be analyzed from the date the most pertinent prior art references. To the contrary, the Examiner stated "there is no showing that others of ordinary skill in the art were working on the problem and if so, for how long." Consequently, Applicants' arguments are moot. The Zauderer reference was merely set forth as an example.

[15] The nature of a problem "which persisted in the art", and the inventor's solution, are factors to be considered in determining whether the invention would have been obvious to a person of ordinary skill in that art. *Northern Telecom Inc. v. Datapoint Corp.*, 908 F.2d 931, 935, 15 USPQ2d 1321, 1324 (Fed. Cir. 1990); *In re Rothermel*, 278 F.2d 393, 397, 125 USPQ 328,

332 (CCPA 1960). Establishing such a long felt need requires objective evidence that the invention has provided a long-awaited, widely accepted, and promptly adopted solution to a problem extant in the art, or that others, had tried but failed to solve that problem. *In re Mixon*, 470 F.2d 1374, 1377, 176 USPQ 296, 299 (CCPA 1973); In re Allen, 324 F.2d 993, 997, 139 USPQ 492, 495 (CCPA 1963).

Applicants state that there was a long-felt need in the art for a method of selecting polynucleotides which encode an antigen-specific human immunoglobulin molecule, or antigen-specific fragment thereof, from eukaryotic cells (e.g., see 2/2/06 Response, page 32, last paragraph). However, there is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. Paragraphs [0003] to [0010], for example, never point to any art-recognized acknowledgment of the problem. That is, there is no evidence that person of skill in the art who was working in the field of phage display or transgenic animals was working on selecting polynucleotides which encode antigen-specific human immunoglobulin molecule, or antigen-specific fragments thereof, from eukaryotic cells. Furthermore, the specification does not indicate that those allegedly attempting to solve the problem were aware of the most relevant prior art (e.g., the Zauderer et al. patent). *In re Sneed*, 710 F.2d 1544, 1549, 218 USPQ 385, 389 (Fed. Cir. 1983). Finally, there is no evidence that any of the people working in the "alternative" technologies switched to the presently claimed method, once the solution to this long-felt need was announced in Applicants published as U.S. Pat. Applic. No. 20020123057. Finally, Applicants must set forth the arguments with specificity (e.g., see *Ex parte Remark* 15 USPQ2d 1498). This has not been done.

Likewise, Applicants' A2 exhibit similarly fails. For example, Applicants' quoted passage on page 29, "We have been evaluating MAb companies for research and therapeutic uses for awhile now and we have yet to make a decision. None of the companies are a clear winner", provides evidence to the contrary. The passage doesn't state what the MAb companies are being evaluated for (i.e., there is no nexus to the currently claimed invention). The passage doesn't state how long "a while" is? The passage doesn't even state that they picked Applicants' technology. If this is a solution to a long-felt need why haven't they made a decision yet?

Applicants also quote the CEO in Exhibit B2 as stating, "Vaccinex's innovative antibody discovery technology will enable us to make a technological leap to develop new fully human antibodies aiming at treating haematological diseases." However, this statement does not equate to evidence that OPi was working on the currently claimed problem and certainly doesn't provide any evidence with regard to how long they were working on the problem. Furthermore, the CEO's statements do not indicate that were aware of the most relevant prior art (e.g., the Zauderer et al. patent). In addition, it's not even clear whether "Vaccinex's innovative antibody discovery technology" is referring to the currently claimed method. That is, OPi's statement doesn't even refer to any of the claimed features such as the use of a vaccinia virus eukaryotic expression system. The failure to solve a long-felt need may be due to factors such as lack of interest or lack of appreciation of an invention's potential or marketability rather than want of technical know-how. *Scully Signal Co. v. Electronics Corp. of America*, 570 F.2d 355, 196 USPQ 657 (1st. Cir. 1977).

Likewise, the statements by the CEO of Lonza Group are similarly deficient. There is no showing Lonza Group was working on the problem and if so, for how long. In addition, there is

no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references; they would still be unable to solve the problem. See MPEP § 716.04. The failure to solve a long-felt need may be due to factors such as lack of interest or lack of appreciation of an invention's potential or marketability rather than want of technical know-how. *Scully Signal Co. v. Electronics Corp. of America*, 570 F.2d 355, 196 USPQ 657 (1st. Cir. 1977).

In the final analysis, evidence of nonobviousness, although being a factor that certainly must be considered, is not necessarily controlling. Newell Companies, Inc. v. Kenney Manufacturing Co., 864 F.2d 757, 768, 9 USPQ2d 1417, 1426 (Fed. Cir. 1988). Based upon the above reasons, the Examiner contends that the preponderance of the evidence weighs in favor of obviousness within the meaning of 35 U.S.C. § 103 based on the totality of the record. See In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

[16] Applicants provide no factual or legal support for this statement and it's not entirely clear what it means? As stated previously, Applicants' arguments are not commensurate in scope with the claimed invention. The Declaration refers only to the system described in the above referenced application and not to the individual claims of the application. As such the declaration does not show that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716. For example, Dr. Zauderer states, "no <u>useful</u> antibodies can be selected in immunoglobulin transgenic animals ... once the antigen-specific variable region is isolated from the phage and expressed as an IgG molecule, it often no longer recognizes the target antigen ... the present invention overcomes these problems (e.g., see Zauderer Declaration, paragraphs 8-10). However, Applicants have already made clear that the

claimed invention is not limited to an "efficient" method for the production of "useful" antibodies. Thus, there was no long felt need to produce antibodies (or fragments thereof) with low binding affinity and/or specificity as these goals were readily obtainable by other means (e.g., see Zauderer Declaration, paragraph 9, "... once the antigen-specific variable region is isolated from the phage and expressed as an IgG molecule, it often no longer recognizes the target", which implies that sometimes it does recognize the target, which obviates Applicants' long felt need argument; see also Zauderer Declaration, paragraph 8, "In some cases ... no useful antibodies can be selected in immunoglobulin transgenic animals", which implies that in other cases usefully antibodies can be obtained, which again obviates Applicants' long felt need argument). That is, Applicants' claims are not limited to an "efficient" method that produces antibodies with a high degree of selectivity and/or affinity. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness. See also section [20] below.

[18] The Examiner respectfully disagrees. Applicants have mischaracterized the holding in *Vaeck*. *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991), involved claims directed to chimeric genes that were toxic to insects such as the larvae of mosquitoes. Previous methods for controlling these insects involved spraying crystalline insecticidal spores over swamps. However, the spores would often sink to the bottom of the swamp before they had a chance to be consumed by the insects, which rendered this method prohibitively expensive. Hence, there was a need for lower-cost methods. The claimed method in *Vaeck* met this need by introducing the chimeric genes into cyanobacteria that, unlike spores, grow on the tops of swamps where they are readily consumed by insects.

The Examiner rejected the claimed invention under 35 U.S.C. § 103(a) based on Dzelzkalns in view of Sekar I or Sekar II and Ganesan. See *Id.* at 1441. Dzelzkalns disclosed a chimeric gene capable of being highly expressed in a cyanobacterium. See *Id.* Sekar I, Sekar II, and Ganesan taught genes encoding proteins in *Bacillus* that were toxic to insects and also provided motivation for expressing these proteins in heterologous systems that provided increased yields. See *Id.* The Examiner thus argued that it would be *prima facie* obvious to substitute the *Bacillus* genes taught by Sekar I, Sekar II, and Ganesan for the chimeric gene disclosed by Dzelzkalns to obtain the sought after increased yields.

In reversing the Examiner's rejection, Judge Rich noted, "it is only in recent years that the biology of cyanobacteria has been clarified ... Such evidence of recent uncertainty regarding the biology of cyanobacteria tends to rebut, rather than support, the PTO's position that one would consider the cyanobacteria effectively interchangeable with bacteria as hosts for expression of the claimed gene." See *Id.* at 1443. That is, when the CAFC assessed the prior art they took into account the high degree of unpredictability surrounding the poorly characterized cyanobacteria to make their obviousness determination. Judge Rich noted that the cyanobacteria had only recently been reclassified as a unique type of bacteria rather than blue-green algae. See *Id.* Thus, it was under these circumstances that the insertion of a Bacillus gene into cyanobacteria was held to be non-obvious. A person of ordinary skill in the art simply wouldn't be able to predict how the cyanobacteria would respond to the introduction of a Bacillus gene given how little was known about these newly classified prokaryotic hosts. That is definitely not the case here. Rowlands et al. state that the use of vaccinia virus as vectors is well known and has wide applications and explicitly state that it can be used for antibody production (e.g., see

Rowland et al., page 4, first full paragraph, "The use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a decade ..."; see also paragraph bridging pages 9 and 10, "the versatility of the method to the present invention means that it will usually be possible to select a type of cell that carries out the processing necessary to produce a fully functional antibody") (emphasis added). Thus, *In re Vaeck* provides strong support for the Examiner's position.

[19] An invention is "obvious to try" where the prior art provides either no indication of which parameters would be critical or no direction as to which of many possible choices is likely to be successful. *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807, 10 USPQ2d 1843, 1845 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989) (quoting *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)).

This is not a situation where there are a large number of possibilities with no expectation of success. Rowlands et al. state that the use of vaccinia virus as vectors is well known and has wide applications and explicitly state that it can be used for antibody production (e.g., see Rowland et al., page 4, first full paragraph, "The use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a decade ..."; see also paragraph bridging pages 9 and 10, "the versatility of the method to the present invention means that it will usually be possible to select a type of cell that carries out the processing necessary to produce a fully functional antibody"). Thus, a person of ordinary skill in the art would know which parameters are critical to express an antibody in a eukaryotic cell. Furthermore, Zauderer provides a facile method for expressing libraries using the same vaccinia virus that is presented in Rowlands et al.

and, a result, one of ordinary skill would also know which parameters are critical to form a library in eukaryotic cells.

[20] Although it is not entirely clear what, if anything, this statement means, the Examiner contends that Applicants are merely trying to set forth a distinction without a difference. Whether Applicants' arguments were directed to the antibodies or the expression libraries it still doesn't change the fact that Applicants' arguments are not commensurate in scope with the claims. For example, independent claim 84, requires both the formation of expression libraries (e.g., see claim 84, step (a), "introducing into a population of mammalian host cells ... a first library of polynucleotides") and the resulting antibodies (e.g., see claim 84, step (c), "permitting expression of immunoglobulin molecules"), which are inextricably linked by the method of translation.

[21] The Examiner respectfully disagrees. Dr. Storkus states, "At the time the idea for the present invention was presented to me, I did not think that antigen-specific antibodies could be efficiently selected from random libraries of immunoglobulin heavy and light chains expressed in eukaryotic cells in vitro because I though specific antibodies of interest would occur at relatively low frequency and it would not be practical to screen the number of eukaryotic cells necessary in order to find a antibody that had a specificity for a specific antigen of interest." (e.g., see Storkus Declaration, page 3). Thus, Applicants interpretation of the Storkus Declaration fails to appreciate the thrust of the argument, namely, that Dr. Storkus was worried about the "relatively low frequency" with which the pairing would occur, not that pairing wouldn't occur at all. Consequently, Applicants' arguments are not consistent with the Declaration.

In addition, as noted previously, the claims do not require "efficient" introduction of libraries into hosts cells or the production of "good" antibodies as Dr. Storkus contends. In fact, Applicants make clear that low efficiency methods that generate poor antibodies are also to be included within the scope of Applicants' claims (e.g., see 12/7/04 Response, page 22, "While the specification does indicate that direct ligation results in a relatively low recombination efficiency and titer ... it does not say that methods such as direct ligation or modified homologous recombination [which are included within the scope of Applicants' invention] cannot be used to generate vaccinia virus expression libraries"; see also page 25, first full paragraph, "... direct ligation and modified homologous recombination may be less efficient than tri-molecular recombination ... [however] the specification does not say that they cannot be used"). Furthermore, there is no requirement that the antibodies "associate properly in the cytoplasm" (e.g., see claim 84 wherein the polypeptides only need be "capable of" combining together) and any underlying facts to support this contention, which have not bee set forth by Dr. Storkus, have been refuted by the combined teachings of Rowlands et al., Zauderer et al. and Waterhouse et al., which clearly sets forth successful examples of the proper association of heavy and light chains (e.g., see page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"). In fact, Applicants' go so far as to state that only "two" antibodies need be produced by the claimed method, which clearly does not constitute a useful screen (e.g., see 12/7/04 Response, page 24, "... claim 84 ... requires expression of a 'plurality' of different immunoglobulins, i.e., two or

more different immunoglobulins" see also footnote 3 on page 24) (emphasis added). Finally, claim 84 states that the polypeptides merely must be "capable" of combining, which explicitly refutes Applicants' assertion that the Storkus reference is commensurate in scope because it talks about "antigen-specific" immunoglobulins that are able to "pair" together. The claims do not require "pairing" because the polypeptides are merely "capable" of it, they don't necessarily undergo said pairing.

[24] Applicants' arguments do not rise to the level of factual evidence. See MPEP § 716.01(c): The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Here, Applicants' statements are entirely unsupported in fact and in law.

Consequently, the Examiner reiterates that Exhibits B2-B4 only serve to highlight this deficiency. For example, Exhibit B2 sets forth, "Vaccinex's technology offers the potential to directly generate fully functional antibodies against difficult targets such as homologous proteins and multi-pass membrane receptors" and Gilles Alberici, CEO of OPi, is quoted as saying, "We are excited about this collaboration with Vaccinex ... Vaccinex's innovative antibody discovery technology will enable use to make a technological leap to develop new fully human antibodies aiming at treating haematological diseases" (e.g., see Exhibit B2, page 1 of 2). However, the Examiner notes that the claims are not limited to "fully functional antibodies" (e.g., see above wherein Applicants' claims, for example, read on "fragments" thereof). In addition, Applicants claims are not limited to antibodies that bind "difficult targets" for treating haematological diseases. In addition, Applicants' claims are not limited to antibodies with "useful" activity or even to antibodies that bind to a target molecule at all (e.g., see 12/7/04 Response, page 24, "...

claim 84 ... requires expression of a 'plurality' of different immunoglobulins, i.e., two or more different immunoglobulins"; see also footnote 3 on page 24). Likewise, Exhibit B3 sets forth, "Vaccinex's innovative library-based antibody discovery technology ... will offer true value to customers by producing substantial quantities of high quality, fully functional human monoclonal antibodies that would have been difficult to identify by other systems." Again, Applicants' claims are not limited to "high quality, fully functional human monoclonal antibodies" (e.g., see above). Furthermore, Exhibit B4 sets forth, "The collaboration combined Vaccinex's capabilities to discover fully human monoclonal antibodies using its proprietary antibody discovery technology ... Vaccinex ... has developed the only library-based antibody discovery platform capable of directly expressing bivalent, fully human antibodies in mammalian cells." Again, Applicants' claims are not limited to "bivalent, monoclonal fully human antibodies" (e.g., see above). In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

[25] Again applicant's arguments do not rise to the level of factual evidence. See MPEP § 716.01(c): The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965).

Applicants have not established a nexus between the claimed invention and the licenses (e.g., see *In re GPAC Inc.* (CAFC) 35 USPQ2d 1116 (6/20/1995), "Licenses taken under the patent in suit may constitute evidence of nonobviousness; however, only little weight can be attributed to such evidence if the patentee does not demonstrate 'a nexus between the merits of the invention and the licenses of record.' Stratoflex, 713 F.2d at 1539, 218 USPQ at 879; see

Demaco, 851 F.2d at 1392, 7 USPQ2d at 1226."). For example, Exhibits B2-B4 do not mention the use of a vaccinia virus (e.g., claim 88), an MOI ranging from about 1 to about 10 (e.g., claim 99), a v7.5/tk virus genome (e.g., claim 107), etc. Thus, it is not clear whether the expression systems to which exhibits B2-B4 refer represent the currently claimed methods.

Furthermore, while no details of the strategic alliances are given, it may very well be, for example, that the competitors decided, for business and/or financial reasons, not to pursue other opportunities. The decision not to pursue one opportunity as opposed to another may be dictated by many factors other than a need for the claimed features of Applicants' invention.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Double Patenting

5. Claims 84, 88-97, 99, 103, 107-122 and 127-131 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-84 of U.S. Patent Application Pub. No. 2003/0104402 A1 (referred to herein as '402) (i.e., Application No. 10/052,942) in view of Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d

1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

Here, claims 1-84 of U.S. Patent No. '402 recite a method for selecting polynucleotides which encode immunoglobulin molecules which is essentially the same as that disclosed by claims 84, 88-97, 99, 103, 107-122 and 127-131 in the present application (e.g., both methods disclose eukaryotic host cells, a first and second library of polynucleotides encoding immunglobulin light/heavy chain constant/variable regions, permitting expression of said immunoglobulin molecules, contacting the molecules with an antigen, recovering the polynucleotides that encode for immunoglobulins that bind to said antigens, etc). The method of claims '402 differ from the present application in that they claim "intracellular" as opposed to "extracellular" expression.

However, Rowlands et al. teach the use of a population of mammalian host cells (e.g., see page 4, paragraph 2; see also paragraph bridging pages 7-8) for introducing and expressing a first/second polynucleotide encoding, through operable association with a transcriptional control region a first/second immunoglobulin polypeptide comprising both heavy/light chain constant/variable regions and a signal peptide for secretion using a vaccinia virus vector i.e., "extracellular" expression (e.g., see claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light

chain has a variable domain at one end and a constant domain at the other end"; see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"). Rowlands et al. do not explicitly state that a "signal" peptide is being used, but the Examiner contends that this feature is inherent in the method disclosed by Rowlands et al. because the fully functional recombinant antibody would not be "secreted" unless it has such a sequence i.e., Rowlands et al. teach "extracellular" expression. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Thus, it would have been obvious to modify the method of claims 1-84 of U.S. Patent Pub. No. '402 such that "extracellular" expression was performed instead of "intracellular" expression because Rowlands et al. teach that "extracellular" expression may be obtained within Applicants' preferred vaccinia virus vector. One having ordinary skill in the art would have been motivated to make such a modification because Rowlands et al. teach that their "extracellular" expression is particularly well suited for

genes of mammalian origin (e.g., see page 4, first full paragraph), which is a preferred embodiment of the '402 patent application (e.g., see claim 26 of '402). In addition, Rowlands et al. teach that their "extracellular" expression techniques are advantageous "particularly in terms of versatility and speed [because] ... [the] virus will infect a wide range of cells [and] ... [thus] Cell lines suitable for production of a recombinant antibody can thus be derived conveniently and quickly. (e.g., see Rowlands et al., paragraph bridging pages 9-10). Furthermore, Rowland et al. teach that "extracellular" screening can be useful in tumor diagnosis and/or analysis (e.g., see page 9, lines 1-4; see also examples wherein Campath antigen is used). Finally, a person of skill in the art would have reasonably expected to be successful because Rowlands et al. explicitly state that the vaccinia virus vectors used in '402 can be manipulated to secrete antibodies (e.g., see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors [i.e., the animal virus disclosed in '402] can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is ***secreted into the medium*** and can thus be recovered in functional form").

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response

6. Applicant's arguments directed to the above double patenting rejection were fully considered but were not deemed persuasive for the following reasons. Please note that the above

rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "One of ordinary skill in the art would not have had a reasonable expectation of success in combining Rowlands with the '402 publication .. Rowlands describes the use of vaccinia virus vectors for making an individual recombinant antibody, not an immunoglobulin expression library" (e.g., see 2/2/06 Response, pages 42 and 43, especially page 43, last paragraph).

[2] Applicants argue, "The Examiner is improperly focusing on the obviousness of differences and substitution in making this rejection rather than on the invention as a whole ... and that it is improper to 'pick and choose from any one reference only so much of it as will support a given position' (e.g., see 2/2/06 Response, pages 43 and 44).

[3] Applicants argue, "if the Examiner is not inclined to withdrawn the rejection, then Applicants respectfully request that it be held in abeyance" (e.g., see 2/2/06 Response, page 44, middle paragraph).

This is not found persuasive for the following reasons:

[1] In response to applicant's arguments against the Rowlands reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the combined references teach the use of libraries as set forth in the rejection above.

[2] The Examiner has considered the references as a whole. Applicants have not pointed to anything in either reference that the Examiner has not fully considered. Furthermore,

Rowlands explicitly or implicitly state that both intracellular and extracelllular antibodies can be used depending on whether or not a signal peptide is used (e.g., see Rowlands, page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form").

[3] The provisional rejection will not be held in abeyance (e.g., see MPEP § 804 B. Between Copending Applications—Provisional Rejections, "The 'provisional' double patenting rejection ***should continue to be made by the examiner*** in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications."). Here, a double patenting rejection is NOT the only rejection remaining in one of the applications and thus the double patenting rejection is proper.

Accordingly, the double patenting rejection cited above is hereby maintained.

New Rejections/Objections

Objections to the Claims

7. Claim(s) 90 is objected to because of the following informalities:

A. Claim 90 contains the misspelled word "visions" in step (q). The Examiner recommends replacing it with "virions." Correction is respectfully requested.

Double Patenting

8. Claims 84, 88-97, 99, 103, 107-122 and 127-131 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 46-128 of U.S. Patent Application 10/465,808 (referred to herein as '808) (US 2005/196755) in view of Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) in view of Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) and Zauderer et al. (WO 00/28016) (Date of Patent is **May 18, 2000**). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

For ***claim 84, 88, 96-97, 113, 117***, the '808 application discloses a method for selecting polynucleotides which encode an antigen-specific human immunoglobulin molecule (e.g., see '808, claim 46). The '808 application also disclose **(a)** introducing into a population of mammalian host cells capable of expressing said immunoglobulin molecule and permissive for vaccinia virus infectivity (e.g., see claim 46, step (a); see also claim 80 disclosing the use of mammalian host cells which would inherently be permissive for vaccinia virus infectivity). The '808 application also discloses a first library of polynucleotides encoding through operable association with a transcriptional control region, a plurality of first immunoglobulin subunit polypeptides (e.g., see '808 application, claim 46, step (a); see also claims 59 and 68 disclosing constant heavy chain

region; see also claims 128). In addition, the '808 application discloses each first immunoglobulin subunit polypeptide comprising **(i)** a first immunoglobulin constant region selected from the group consisting of a heavy chain constant region and a light chain constant region (e.g., see '808, claim 46 claim 128, step (a)(i)). The '808 application also discloses **(ii)** an immunoglobulin variable region selected from the group consisting of a heavy chain variable region and a light chain variable region wherein said variable region corresponds to said first constant region (e.g., see '808, claim 46(a)(ii);). The '808 application also discloses **(iii)** a signal peptide capable of directing cell surface expression or secretion of said first immunoglobulin subunit polypeptide (e.g., see '808 claim 46(a)(iii)). The '808 application also discloses **(b)** introducing into said host cells a second library of polynucleotides encoding through operable association with a transcriptional control region a plurality of second immunoglobulin subunit polypeptides each comprising (e.g., see '808, claim 46(b); see also claim 80). In addition, the '808 application discloses **(i)** a second immunoglobulin constant region selected from the group consisting of a heavy chain constant region or a light chain constant region wherein said second immunoglobulin constant region is not the same as said first immunoglobulin constant region (e.g., see '808, claim 46(b)(i)). The '808 application also discloses **(ii)** an immunoglobulin variable region selected from the group consisting of heavy chain variable region ad a light chain variable region, wherein said variable region corresponds to said second constant region (e.g., see '808, claim 46(b)(ii). The'808 application also discloses **(iii)** a signal peptide capable of directing cell surface expression or secretion of said second immunoglobulin subunit (e.g., see '808, claim 46(b)(iii)). The '808 also

discloses said second immunoglobulin subunit polypeptide that is capable of combining with said first immunoglobulin polypeptide to form an immunoglobulin molecule (e.g., see claim 46(b)(iii)). Finally, the '808 application teaches (c)-(e) permitting expression of immunoglobulin molecules, contacting said immunoglobulin molecules with an antigen, detecting specific antigen-antibody complexes and recovering polynucleotides of said first library which encode immunoglobulin subunit polypeptides (e.g., see claim 46(b)(iii)).

For ***claims 89-91***, the '808 application disclose repetitive steps for "biopanning" a library (e.g., see '808, 48, 52, 115 and 123).

For ***claims 92-95***, the '808 application disclose "isolating" steps (e.g., see '808, see claims 49 and 53).

For ***claim 99***, the '808 application also discloses an MOI of 1 to 10 (e.g., see '808, claim 76).

For ***claim 103***, the '808 application also disclose T7 promoter (e.g., see '808 application, claim 96).

For ***claim 107, 110, 127-131***, the '808 application disclose method steps for "tri-molecular" recombination (e.g., see '808, claim 98, 99 and 128).

For ***claims 114-116, 118-120***, the '808 application disclose the use of virus "pools." (e.g., see '808, claims 113, 114, 119, 121)

The '808 differs from the claimed invention as follows:

For ***claim 84***, '808 fails to disclose the use of a vaccinia virus. The 808 application only discloses the use of a eukaryotic virus vector such as a poxvirus vector vector (e.g., see '808, claims 72, 73, 78, 79 and 85-88).

For ***claims 108-109, 111-112***, the '808 application fails to disclose v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction sites.

For ***claims 121-122***, the '808 application fail to disclose ELISA (e.g., see page 18, line 7).

However, Rowlands et al. and Zauderer et al. teach the following limitations that are deficient in abc et al.:

For ***claim 84***, Rowlands et al. and Zauderer et al. (see entire documents) teach the use of vaccinia virus. For example, Rowlands et al. teach a method for producing antibodies in vaccinia infected cells that reads on the presently claimed invention (e.g., see Rowlands et al., abstract). Furthermore, Rowlands et al. teach the use of a population of mammalian host cells (e.g., see page 4, paragraph 2; see also paragraph bridging pages 7-8) for introducing and expressing a first/second polynucleotide encoding, through operable association with a transcriptional control region a first/second immunoglobulin polypeptide comprising both heavy/light chain constant/variable regions and a signal peptide for secretion using a vaccinia virus vector (e.g., see claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has

at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end"; see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"; see also page 6, paragraphs 1 and 2). Rowlands et al. do not explicitly state that a "signal" peptide is being used, but the Examiner contends that this feature is inherent in the method disclosed by Rowlands et al. because the fully functional recombinant antibody would not be "secreted" unless it has such a sequence. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, Rowlands et al. disclose contacting said immunoglobulin molecules with an antigen and detecting specific antigen-antibody complexes (e.g., see pages 18-19 and Table I wherein the Campath 1H antigen was "contacted" with said immunoglobulin molecules and "detection" was carried out using both T-cell and antigen binding assays). Finally, Rowlands et al. disclose recovering the vaccinia virus vectors containing polynucleotides of said first library which encode immunoglobulin subunits polypeptides which, as part

of an immunoglobulin molecule are specific for said antigen (e.g., see page 5, paragraph 1, step 4, wherein the virus is "harvested" several times [i.e., recovered and/or isolated]).

In addition, Zauderer et al. (see entire documents) teach the use of a "library" of polynucleotides in a vaccinia virus vector using the "tri-molecular recombination" approach for screening purposes (e.g., see Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52). In addition, Waterhouse et al. teach that a "library" can be usefully employed to screen for antibodies with high affinity to various antigens including the use of heavy/light chains that are "packaged together" i.e., two libraries (see Waterhouse et al., page 2265, column 1; see also paragraph bridging pages 2265-2266, "... creation of extremely large combinatorial repertoires [is possible]... for example by providing a light chain repertoire in A [i.e., library number 1] and a heavy chain repertoire in B [i.e., library number 2]"). The Examiner further notes that Applicants' elected mammalian "HeLa" cells are disclosed also by Zauderer et al. (e.g., see Zauderer et al., page 32, line 2).

For ***claims 89-91***, Zauderer et al. also disclose the use of vaccinia virus library vectors that require the use of a helper virus (i.e., are "incapable of producing infectious vaccinia virus") to infect host cells (e.g., see Zauderer et al., paragraph bridging pages 97-98, "Vaccinia virus DNA is not infectious as the virus cannot utilize cellular transcriptional machinery ... Previously ... non-homologous poxvirus fowlpox ... have

been utilized as helper virus for packaging"). Zauderer et al. also indicate that the steps for introducing said vectors into host cells, permitting the expression of said vectors, contacting said expressed antibodies with an antigen and recovering said vectors can be repeated as needed to increase the specificity and/or binding affinity (e.g., see page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure").

For ***claims 92-95***, Zauderer et al. also disclose "isolating" the polynucleotides contained in the vaccinia virus vectors (e.g., see Zauderer et al., page 52, lines 20-23; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

For ***claim 99***, Zauderer et al. also disclose, for example an MOI = 1 (e.g., see page 86, line 2).

For ***claim 103***, Rowlands et al. also disclose a T7 phage promoter active in cells in which T7 RNA polymerase is expressed (e.g., see page 8, paragraph 2, "Expression levels of the two chains of the antibody can be enhanced by use of T7 polymerase to amplify the gene under the control of the T7 promoter").

For ***claims 107, 110, 127-131***, Zauderer et al. also disclose "tri-molecular" recombination, which includes, for example, cleavage of v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction enzymes and "one" transfer plasmid containing TKL/TKR and a library of human immunoglobulin genes containing both heavy and light genes to form

vaccinia virus vectors via homologous recombination and method steps for screening and purifying said vectors repeated as many times as are needed to produce the desired products (e.g., see pages 48-52, sections 5.2-5.3; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]"; see also claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter").

For ***claims 108, 111***, Zauderer et al. disclose both v7.5/tk and vEL/tk (e.g., see figure 1).

For ***claims 109, 112***, Zauderer et al. disclose both NotI and ApaI (e.g., see figure 10).

For ***claims 114-116, 118-120***, Zauderer et al. also disclose the use of "virus pools" (e.g., see page 51, last paragraph, especially line 27; see also page 58, Table V wherein multiple cycles are disclosed; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

For ***claims 121-122***, Rowlands et al. disclose ELISA (e.g., see page 18, line 7).

It would have been *prima facie* obvious to one of ordinary skill in the art to select vaccinia virus as taught by the combined references of Zauderer et al. and Rowlands et al.

as the eukaryotic virus vector as taught by the '808 patent application because Zauderer et al. explicitly state that their libraries can be efficiently produced using the tri-molecular recombination approach with the vaccinia virus vectors (like the vaccinia virus vectors disclosed by Rowlands et al.). Thus, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. and the'808 application because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"; see also Rowlands et al., page 4, paragraph 2, "One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian origin"). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Zauderer et al. teach several successful examples of library formation using the same vaccinia virus vectors that are disclosed by Rowlands et al. and the '808 application. Furthermore, a person of ordinary skill in the art would reasonably have expected to be successful because Rowlands et al. state that the use of vaccinia virus as vectors is well known and has wide applications and explicitly state that it can be used for antibody production (e.g., see Rowland et al., page 4, first full paragraph, "The use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a

decade ..."; see also paragraph bridging pages 9 and 10, "the versatility of the method to the present invention means that it will usually be possible to select a type of cell that carries out the processing necessary to produce a fully functional antibody") and also provide successful examples of antibody expression using vaccinia.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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April 14, 2006

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PATENT EXAMINER